Timing of delivery for women with non-severe hypertensive disorders of pregnancy

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Chapter 1

General introduction and outline
General introduction

Hypertensive disorders of pregnancy
The term “hypertensive disorders of pregnancy” covers a spectrum of disorders characterised by hypertension during pregnancy. At present, four main disorders are usually distinguished, depending on the timing of hypertension relative to pregnancy and on the presence or absence of proteinuria and/or other systemic symptoms (table 1):¹

Table 1. Hypertensive disorders of pregnancy; classification

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Proteinuria⁴/ other systemic symptoms⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational hypertension</td>
<td>≥20 weeks of gestation</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>≥20 weeks of gestation</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>&lt; pregnancy OR &lt;20 weeks of gestation</td>
</tr>
<tr>
<td></td>
<td>not resolving after pregnancy</td>
</tr>
<tr>
<td>Superimposed</td>
<td>&lt; pregnancy OR &lt;20 weeks of gestation</td>
</tr>
<tr>
<td>pre-eclampsia</td>
<td>not resolving after pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹Blood pressure ≥ 140/90 mmHg, or ≥ 90 mmHg diastolic only
²Usually ≥1+ on dipstick, random protein:creatinine ≥30 mg/mmol, or 24 hour protein ≥ 300mg/L
³Maternal symptoms, fetoplacental abnormalities, abnormal laboratory findings

HELLP syndrome (Hemolysis, Elevated Liver enzymes and Low Platelets syndrome) is sometimes classified as an independent hypertensive disorder, but is now generally considered a specific combination of systemic symptoms and therefore a subtype of pre-eclampsia or superimposed pre-eclampsia.

Hypertensive disorders of pregnancy occur in approximately 10% of all pregnancies, depending on the exact definitions used and the population studied.²¹³ They are associated with 10% of maternal mortality,¹⁴ with 9-60% of obstetric intensive care admissions,¹⁵ and with one fifth up to two thirds of the general obstetric admissions.¹⁶ In addition, hypertensive disorders of pregnancy are associated with foetal and neonatal morbidity and mortality. For example, 4-9% of stillbirths are associated with hypertensive disorders of pregnancy,¹⁷ as are up to 25% of all preterm births.¹⁸
Managing hypertensive disorders of pregnancy
The origin of the hypertensive disorders of pregnancy is thought to be placental. But although much progress has been made over the last years, the pathophysiology of the hypertensive disorders of pregnancy is still not fully understood. As a consequence, causal treatments are limited and the only currently available is delivery of the placenta and, inevitably, of the child. This halts progression of the disorder and therefore has the potential to prevent maternal and neonatal morbidity and mortality. However, delivery also has potential disadvantages. Depending on the gestational age at diagnosis, immediate delivery can imply preterm or early term delivery, which is associated with an increased risk of neonatal morbidity and mortality. In addition, induction of labour was still believed to increase the risk of caesarean section when the work described in this thesis started. And caesarean section is associated with an increased risk of maternal complications and complications in future pregnancies. Therefore the management of hypertensive disorders of pregnancy revolves around balancing the risks of allowing the pregnancy to continue against the risks of delivery, as depicted in figure 1.

When considering this balance, it is important to realise that maternal health does not benefit from expectant monitoring. And as maternal health is the first priority, expectant monitoring should only be considered if there is a chance of improving neonatal outcomes without increasing maternal risk. Therefore, the balance starts out leaning towards delivery, with its final position depending on two factors. First, the presence or absence of severe features, either maternal or foetal, determines how much further the balance leans towards delivery. Second, the gestational age: before neonatal viability (<24 weeks), the period during which substantial neonatal morbidity is expected (24-34 weeks), the period during which mild neonatal morbidity is expected (34-37 weeks), and the period when the risk of neonatal morbidity is expected (34-37 weeks), and the period when the risk of neonatal morbidity is expected (34-37 weeks).
morbidity is low (≥37 weeks). This determines how much can be gained from expectant monitoring and thus how much weight there is on the side of expectant monitoring.

For women with severe hypertensive disorders of pregnancy, expectant monitoring is only considered between 24 and 34 weeks of gestation, after a period of 48 hours during which corticosteroids to accelerate fetal lung maturation are administered. If no indication for emergency delivery has occurred within this period, expectant monitoring until 34 weeks is an option. A meta-analysis of randomised controlled trials has shown that although this strategy increases the risk of fetal growth restriction, the effect on other types of neonatal morbidity seems favourable and the effect on maternal outcomes equivocal. Before 24 weeks, expectant monitoring does not improve the high perinatal mortality rate, tipping the balance towards delivery. After 34 weeks, delivery is expected to result in relatively mild neonatal morbidity, which also tips the balance towards delivery.

For women with non-severe hypertensive disorders of pregnancy, delivery is generally not considered before 34 weeks. However, the possibility that progression to a severe hypertensive disorder might occur rapidly, especially at lower gestational ages, warrants vigilance and preparing for delivery in the near feature. There is less consensus about the best strategy for women with non-severe hypertensive disorders after 34 weeks of gestation. There is discussion about which maternal outcomes should be classified as “adverse” and against which neonatal outcomes they should be weighed. Is preventing the development of HELLP syndrome enough to justify delivery between 34 and 37 weeks of gestation? Is preventing the development of severe hypertension enough to justify delivery after 37 weeks? Is preventing relatively mild neonatal problems like feeding difficulties enough reason to justify expectant monitoring? Should long-term paediatric outcomes be taken into the equation? Should a distinction be made between the different hypertensive disorders of pregnancy? These questions are difficult, and the answers given by different study groups do not only depend on scientific facts and personal opinions, but also on feasibility.
Timing of delivery for women with non-severe hypertensive disorders of pregnancy

The first randomized trial focusing on this grey area was the HYPITAT study, retrospectively called HYPITAT-I. In this study, immediate delivery was compared with expectant monitoring for women with mild hypertensive disorders of pregnancy at or beyond 36 weeks of gestation. The primary outcome was a composite of adverse maternal outcomes including maternal mortality, eclampsia, HELLP syndrome, pulmonary oedema, thromboembolic disease, placental abruption, major post-partum haemorrhage or progression to severe disease. This outcome occurred significantly less frequent in women who were randomised for delivery as compared to women who were monitored expectantly (31% vs. 44%, relative risk (RR) 0.71, 95% confidence interval (CI) 0.59–0.86). The risk of adverse neonatal outcomes (5 minute apgar score below 7, umbilical artery pH below 7.05, or admission to a neonatal intensive care unit), which was a secondary outcome in this study, did not differ between the two randomized groups (6% vs. 8%, RR 0.75 (0.45-1.26)). Neither did the risk of caesarean section, which was a secondary outcome as well (14% vs. 19%, RR 0.75 (0.55-1.04)). As only a few women with a gestational age between 36 and 37 weeks were included, the authors concluded that delivery should be advised for women with mild hypertensive disorders from 37 weeks of gestation onwards.

After this study, questions concerning the issue of delivery versus expectant monitoring for women with non-severe hypertensive disorders of pregnancy remained. First, it was unclear whether delivery or expectant monitoring should be advised for women with non-severe hypertensive disorders of pregnancy at an earlier gestational age, between 34 and 37 weeks. Another subgroup for whom the question of delivery versus expectant monitoring was still standing was the group of women with stable chronic hypertension at or beyond 37 weeks of gestation, who were excluded from HYPITAT-I. Other remaining questions were whether a distinction should be made between different hypertensive disorders, and whether other factors related to the mother, the unborn child, or the pregnancy, influence the balance between delivery and expectant monitoring.
Chapter 1

Aim of this thesis
The aim of the research described in this thesis was to contribute towards solving the dilemma of immediate delivery versus expectant monitoring for women with non-severe hypertensive disorders of pregnancy. The questions in the previous paragraph functioned as guide. Therefore, the first part of this thesis focuses on the HYPITAT-II study, which assessed immediate delivery versus expectant management for women with non-severe hypertensive disorders between 34 and 37 weeks of gestation. The second part touches upon some of the other remaining questions. It contains a cohort study on gestational age specific pregnancy outcomes among women with chronic hypertension. It also contains a description of the relevance of individual patient data meta-analysis for studies in obstetrics, using the question of immediate delivery versus expectant monitoring for women with non-severe hypertensive disorders of pregnancy as an example.

Outline

PART I. IMMEDIATE DELIVERY VERSUS EXPECTANT MONITORING FOR WOMEN WITH NON-SEVERE HYPERTENSIVE DISORDERS OF PREGNANCY BETWEEN 34 AND 37 WEEKS OF GESTATION: HYPITAT-II
Chapter two describes the protocol for the HYPITAT-II study, a randomised controlled trial comparing immediate delivery with expectant monitoring for women with non-severe hypertensive disorders of pregnancy between 34 and 37 weeks of gestation. It also contains a correction that was published after the study had been funded. Chapter three contains the main outcomes of the HYPITAT-II study. Results of the quality of life study that was performed alongside the study are described in chapter four, and results of the economic analysis that was also conducted alongside it are described in chapter five. Finally, chapter six describes a secondary analysis focussing on prediction of progression to severe disease, using data of women who were monitored expectantly in the HYPITAT-II study.
PART II. GENERAL ASPECTS OF DELIVERY VERSUS EXPECTANT MONITORING FOR WOMEN WITH NON-SEVERE HYPERTENSIVE DISORDERS OF PREGNANCY

In chapter seven, a cohort study on gestational age specific pregnancy outcomes among women with chronic hypertension is described. This study was performed in preparation for a randomised controlled trial on delivery versus expectant monitoring for women with stable chronic hypertension at or beyond 37 weeks of gestation. Chapter eight describes the relevance of individual patient data meta-analysis (IPDMA) for studies in obstetrics in general, and for studies on delivery versus expectant monitoring specifically. It details how this type of study can overcome some of the challenges with regard to choosing relevant outcome measures and studying a clinically heterogeneous study population. This chapter was written in preparation for an actual IPDMA on immediate delivery versus expectant monitoring for women with non-severe hypertensive disorders of pregnancy. This study is ongoing; the protocol is included as appendix to chapter eight. Chapter nine contains the general discussion and future perspectives. This chapter puts the work described in this thesis in the context of current clinical practice. It also describes how ongoing developments in the management of hypertensive disorders of pregnancy might influence the meaning of this work in the near future.
Chapter 1

References


Part I

HYPITAT-II: delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation